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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,687	07/27/2001	Barbara J. Wold	CIT1410-1	2185

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,687	WOLD ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant argues that the kits should be rejoined with the methods because there is no separate search and consideration. This is simply not correct, since the consideration and search for Kits is significantly different for methods since the intended uses of the kits carry no patentable weight. Further, as noted in the restriction, the groups are independent and distinct and the separate classification is prima facie evidence of search burden.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-28, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al (U.S. Patent 6,043,031) in view of Montforte et al (U.S. Patent 6,635,452).

Koster teaches a method of claims 1, 9, 20, 28, and 31, of detecting a specific nucleic acid in a sample (see column 3, lines 47-57) comprising:

(a) contacting the nucleic acid with a first oligonucleotide linked to a selector tag (see column 24, lines 8-10 and column 24, lines 24-50, where a first oligonucleotide was linked to biotin)

and a second oligonucleotide linked to a detector tag (see figures 3 and 5, column 6, lines 59-67 and column 14, lines 27-67, where one of the LCR oligonucleotides can be attached to a mass modifying functionality to enhance detection),

in a reaction mixture under conditions that allow the first and second oligonucleotides to specifically hybridize with the nucleic acid such that the first

oligonucleotide is located immediately adjacent to the second oligonucleotide, thereby forming adjacently hybridized first and second

oligonucleotides (see column 24, lines 33-58, figure 5 and figures 30-33),

(b) ligating the adjacently hybridized first and second oligonucleotides to form a ligated oligonucleotide (See figures 3 and 5 and column 24, lines 39-58)

(c) identifying the detector tag associated with the ligated oligonucleotide thereby detecting a specific nucleic acid in a sample (see figures 30-33, column 14, lines 27-67 and column 24, line 60 to column 227, line 58).

With regard to claims 2-3, 10-11, 21-23, Koster teaches separation of the ligated oligonucleotide using the biotin selector tag (see column 25, lines 4-15 and figures 3 and 5).

With regard to claim 5, 13, 27, Koster teaches detection using MALDI-TOF mass spectrometric measurements (see column 25, lines 38-51).

With regard to claim 6, 14, Koster teaches the use of HPLC chromatography for separation and detection (see column 24, lines 60-67).

With regard to claim 7, 15, 25, 32, Koster teaches a biotin selector tag (see column 25, lines 4-15).

With regard to claim 8, 16, 26, 32, Koster teaches the use of oligoglycine (a peptide) as a mass modifier (which is the detector moiety) (see column 15, lines 16-21).

With regard to claims 17-19, Koster teaches multiplex assays (see column 14, lines 14-30) with the use of different detector tags (see column 14, lines 14-30) or by use of different capture sequences (see column 15, lines 45-55).

Koster does not teach the step of de-linking the mass label for detection.

Montforte teaches methods for releasing mass labels for detection prior to spectrometric analysis (see column 24, lines 30-65). With regard to claims 4, 12, and 24, Montforte specifically teaches delinking by use of heat, enzyme and light (see column 24, lines 40-41). Montforte further teaches LCR (see column 31, lines 4-15) and the use of specific capture (see column 46).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Koster to release the mass label for detection since Montforte expressly teaches the use of this method with ligase chain reaction (see column 31, lines 4-15) and since Montforte notes "In some embodiments, it may be important to release the mass label from all or most of the reactive group prior to

spectrometric analysis, as represented in FIG. 11 for a mass-labeled nucleic acid probe. (see column 24, lines 32-35). Montforte further notes "As another option, analysis of mass-labeled nucleic acid probes by MALDI

mass spectrometry may be performed using a matrix that selectively desorbs and efficiently ionizes intact released mass labels but not mass labels still

coupled to their respective nucleic acid probes. Nucleic acid molecules often do not desorb well in many matrices which are yet effective for the desorption

of released mass labels, and this difference can be accentuated by the presence of impurities such as salts. Mass-labeled nucleic acid probes may typically be analyzed by direct laser-desorption mass spectrometry without further purification if, for example, the released mass label(s) are detected much more

efficiently than unreleased labels. The same holds true for other forms of mass spectrometry. Thus, in a preferred embodiment using laser-desorption mass spectrometry, physical partitioning of the released and unreleased mass labels may not be required. (see column 29, lines 47-62)." An ordinary practitioner would have been motivated to use releasable mass labels in the method of Koster since Montforte expressly suggests that in Mass Spectrometric methods involving nucleic acids, it is sometimes desirable to release the mass label since the nucleic acid molecules do not always desorb well.

4. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al (U.S. Patent 6,043,031) in view of Montforte et al (U.S. Patent 6,635,452) and further in view of Kinzler et al (U.S. Patent 5,695,937).

Koster in view of Montforte teaches the limitations of claims 1-28 and 31-32 as discussed above. Koster in view of Montforte does not teach alternate separation moieties such as capture using polyA tails or 5' capped nucleic acids.

Kinsler teaches "For example, as illustrated in the present EXAMPLES, streptavidin beads are used to isolate the defined 3' nucleotide sequence tag when the oligo dT primer for cDNA synthesis is biotinylated. In this example, cleavage with the first or anchoring enzyme provides a unique site on each transcript which corresponds to

the restriction site located closest to the poly-A tail. Likewise, the 5' cap of a transcript (the cDNA) can be utilized for labeling or binding a capture means for isolation of a 5' defined nucleotide sequence tag. Those of skill in the art will know other similar capture systems (e.g., biotin/streptavidin, digoxigenin/anti-digoxigenin) for isolation of the defined sequence tag as described herein (see column 4, line 67 and column 5, lines 1-12)." So Kinsler teaches that 5' caps and poly-A tails captured with oligo dT are equivalents to biotin/streptavidin (see column 5, lines 1-12).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Koster in view of Montforte to use the equivalent capture methods of polyA tails and 5' caps taught by Kinsler since Kinsler expressly notes that these are equivalent capture systems for isolation of nucleic acids (see column 5, lines 1-12). As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot

be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Here, there is an express suggestion to substitute equivalents in Kinsler, which further motivates the use of the capture moiety which best fits the desired conditions or desired costs.

Response to Arguments

5. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection which address the newly added limitation. It is expressly noted that claims 4, 12 and 24 did NOT require delinking previously and were properly rejected under 102. Further, these claims would not provide basis for de linking of the tag from the nucleic acid since they were solely directed towards removing the detector tag which could be broadly read to simply include removing the detector tag from the solid support, but the specification does have basis for the new limitation. Consequently, this action is properly made final as necessitated by amendment.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634